70. (Original) The method of claim 59, wherein the expression vector is a plasmid or a virus for expression in non-bacterial host cells.

71. (Original) The method of claim 60, wherein the expression vector is a plasmid or a virus for expression in non-bacterial host cells.

72. (Original) The method of claim 61, wherein the expression vector is a plasmid or a virus for expression in non-bacterial host cells.

REMARKS

A check for the requisite fees for filing an RCE and for a three month extension of time accompanies this response. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 50-1213. A Supplemental Information Disclosure Statement accompanies this Preliminary Amendment and Request for Continued Examination.

Claims 8-14 and 58-72 are pending in this application. Claims 58 and 59 are amended to correct minor typographical and grammatical errors, or to provide proper antecedent basis.

Claim 8 is amended to more particularly point out the claimed subject matter. As amended, Claim 8 more clearly recites that in the claimed method of assigning function to a product encoded by a nucleotide sequence of a sample nucleic acid, the oligonucleotide family is directly delivered, amplified and expressed in a host cell containing the sample nucleic acid, without prior cloning (in a cell other than the host cell, such as a bacterial cell) or amplification of the oligonucleotide family constructs. As discussed below, previous methods to elucidate gene function(s) involved several bacterial or bacteriophage cloning and subcloning steps for isolating and manipulating nucleic acids before they were introduced into a host cell to characterize gene(s) of interest expressed therein. This was a significant limitation, in terms of time and expense.

Moreover, the prior bacterial cloning steps or amplification steps rendered high throughput genetic analysis impractical. The instant method carries out the steps of delivery, amplification and expression of a nucleic acid family directly in the cell containing the gene to be analyzed. This "single host method" of performing the delivery, amplification and expression steps of a nucleic acid family directly in the host cell containing the gene to be analyzed, renders the method amenable to high throughput screening.

As disclosed in the instant application (*e.g.*, at page 6, lines 9-22), bacterial cloning and amplification of plasmid DNA prior to its introduction and expression in a target cell (like a tumor cell, *see*, *e.g.*, page 15, lines 3-23) can be time-consuming and cost prohibitive. For example, *E. Coli* amplification can add several days to the method. By avoiding prior amplification steps, the instant method is amenable to high throughput formats where a large number of expression vectors containing a family of nucleic acids are constructed in a matrix format and simultaneously introduced into a matrix of cell cultures containing one or more host cells expressing one or more target nucleic acids that contain the sample nucleic acid encoding a gene of interest (*see*, *e.g.*, page 3, lines 10-22; page 5, lines 21-27). The family is expressed as transcripts in non-bacterial host cells by **direct** delivery and amplification in the non-bacterial host cells (*see*, *e.g.*, Summary; page 4, lines 27-29; and page 13, lines 18-22 of the specification). The oligonucleotide family, usually present in a suitable vector, is not subjected to a bacterial cloning step or an amplification step prior to being introduced into the target cell expressing the gene of interest. The members of this oligonucleotide family are expressed as individual transcription products in a host cell, bind to mRNA from a target nucleic acid molecule containing the sample nucleic acid sequence and phenotypic changes within the resulting host cells are detected and analyzed (see, *e.g.*, page 3, lines 13-26; page 4, line 32, through page 5, line 3; page 15, line 3, through page 17, line 2; Example 4, beginning at page 19, line 6; and Example 7, beginning at page 20,

line 24). The phenotypic changes are then correlated to a corresponding change in function, which in turn is assigned to the product encoded by the sample nucleic acid sequence.

No amendments have been made to obviate prior art and no new matter has been added.

THE REJECTION OF CLAIMS 8-14 AND 58-72 UNDER 35 U.S.C. §102(e)

The rejection of Claims 8-14 is maintained and Claims 58-72 are rejected under 35 U.S.C. §102(e) as being anticipated by Beach *et al.* (U.S. Patent No. 6,255,071), for reasons of record in the previous Office Action. In the previous Office Action, it was alleged that Beach *et al.* anticipates the instant claims because it allegedly discloses methods for the identification and isolation of nucleic acid molecules based upon their ability to complement a mammalian cellular phenotype, antisense-based methods for the identification and isolation of nucleic acid sequences which inhibit the function of a mammalian gene, and gene trapping methods for the identification and isolation of mammalian genes that are modulated in response to specific stimuli.

The Examiner contends that Applicant's previous arguments stating that unlike the instant claims, Beach *et al.* does not disclose a method of assigning a heretofore unknown function to a product encoded by a target nucleic acid of known sequence, are unpersuasive for the following reasons:

1) It is alleged that, contrary to Applicant's assertions, the antisense methods disclosed in Beach *et al.* includes those methods that do not rely on direct selection of a gene function, *i.e.*, where the corresponding phenotype is unknown. These methods of Beach *et al.* allegedly include identifying sequences that affect heretofore unknown phenotypes of loss-of-function mutations (col. 22, lines 30-39; Example 15, col. 48); and isolating new nucleic acid sequences based on the observation that loss of an unknown gene produces a particular phenotype (col. 24, lines 17-34).

2) The Examiner further alleges that as stated in the previous Office Action, Beach *et al.* also discloses assignment of function to genes based on an observable known phenotype. These methods of Beach *et al.* allegedly include assigning a function to heretofore unknown nucleic acid sequences that modulate an observable phenotype such as cell survival (col. 27, lines 50-67) or telomerase activity (col. 48, line 54 to col. 49, line 20).

This rejection is respectfully traversed.

Summary of Arguments

A) As discussed below, Beach *et al.* does not disclose any method of assigning function to a product encoded by a known nucleic acid sequence in which an oligonucleotide family (library) is directly expressed and amplified in a target cell expressing the known nucleic acid sequence, without prior (intervening) bacterial cloning steps or prior amplification steps. Beach *et al.* is directed to methods for the identification and isolation of nucleic acid molecules based upon their ability to modulate the function of various known or unknown cellular genes. In some of these methods of Beach *et al.*, libraries of nucleic acids (rather than a single test sequence) are tested for their ability to modulate cellular function. **The libraries generated in Beach *et al.* are all cloned into bacterial cells and/or amplified before expressing them in target cells or organisms.**

On the other hand, the library constructs containing the oligonucleotide families of the instantly claimed methods are directly transfected into the target non-bacterial host cells that contain the gene to be analyzed. In fact, the absence of a bacterial cloning step or any prior amplification step is one of the advantages of the claimed methods of the instant application, providing savings in cost and time (*see, e.g.*, page 4, lines 27-29; page 13, lines 18-22). Unlike the methods disclosed in Beach *et al.*, in the instant methods, the family of nucleic acids used to identify gene function are ligated into a suitable vector, then immediately introduced into the target cell(s) that contain the gene(s) to be

analyzed (*see, e.g.*, page 3, lines 10-22; page 4, lines 27-29; page 5, lines 21-27). Delivery, amplification and expression for genetic analysis are all carried out in a single system, avoiding prior bacterial (or other cellular) cloning steps and amplification steps. As described, *e.g.*, at page 13, lines 18-22 of the instant specification, this direct amplification and expression in the non-bacterial target cells provides distinct advantages of savings in time and expense.

B) Moreover, as discussed previously (Amendment and Response filed May 7, 2003) and below, and as the Examiner has acknowledged above, the methods in Beach *et al.* identify new oligonucleotide sequences as potential modulators of cellular function (*e.g.*, for therapeutics), whether such function or its associated phenotype is previously known or unknown. Regardless of whether the phenotype is known (*i.e.*, can be directly correlated with gene function) or unknown (*i.e.*, the gene function cannot be selected "directly"), Beach *et al.* newly identifies sequences that modulate gene function. Beach *et al.* discloses ways of modulating gene function in cells, whether the genes are associated with known (observable) phenotypes or whether the associated phenotypes are unknown. Unlike the instant methods, Beach *et al.* does not disclose any method of assigning function to products encoded by known sequences, such as sequences of genes, gene fragments and essential sequence tags (ESTs) contained in sequence databases compiled from various genome sequencing projects.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims

measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter *is* identically disclosed or described in the "'prior art'" . . .the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a 103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a 102, anticipation rejection." (Emphasis in original). *In re Arkey, Eardly, and Long*, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

Claims

Claim 8 is directed to a method for assigning function to the product of a sample nucleotide sequence. The steps of the method include:

> a) without any intervening bacterial cloning steps, delivering into and amplifying and expressing one or more members of an oligonucleotide family as individual transcription products in a plurality of recombinant non-bacterial host cells comprising a target nucleic acid molecule that comprises the nucleotide sequence of the sample nucleic acid, wherein:
>
> the coding sequences for each individual transcription product encodes an antisense nucleic acid that, when

expressed as RNA, binds to mRNA transcribed from the target nucleic acid molecule that comprises the nucleotide sequence of the sample nucleic acid; and

expression of one or more of the individual transcription products inhibits production of a product of the mRNA; and

b) in the resulting host cells, analyzing phenotypic changes to thereby identify a corresponding change in function, whereby, based upon the corresponding change in function, a function is assigned to the product encoded by the nucleotide sequence of the sample nucleic acid.

Dependent claims 9-14 specify particulars, such as the nature of the function (*e.g.*, a physiological function, an enzymatic function, protein synthesis, expression of a biological factor or a regulatory effector function) and whether the function is changed directly. Dependent claims 58-72 specify particulars, such as the introduction of members of the oligonucleotide family into an expression vector (*e.g.*, a plasmid or a virus), the type of sample nucleic acid (*e.g.*, genomic DNA, cDNA, an EST or RNA) or that the methods are performed in high-throughput format.

Thus, all of the instantly claimed methods are directed to assigning a function to a product encoded by a target nucleotide sequence in which members of an oligonucleotide family are directly introduced, amplified and expressed in a non-bacterial host cell containing the target sequence of interest ("target cell"). There is no prior manipulation of the oligonucleotide family by, *e.g.*, cloning in bacteria or a cell other than the target cell, or an amplification step. Beach *et al.* does not disclose any method in which an oligonucleotide family (*e.g.*, a constructed library) is directly introduced into a target non-bacterial cell of interest, with no prior bacterial cloning and/or amplification. Beach *et al.* does not disclose any method where the steps of delivery, amplification and expression of an oligonucleotide family are all carried out in

the cell containing the gene to be analyzed, without any prior amplification, cellular or otherwise.

Further, all of the instantly claimed methods are directed to assigning a function to a nucleotide sequence of a sample nucleic acid. The claimed methods assign a previously unknown function to a sample nucleic acid sequence based on detection and analysis of a cellular phenotypic change. Beach *et al.* does not disclose any method of assigning a heretofore unknown function to a product encoded by a sample nucleic acid sequence by measuring an observable phenotype that can be correlated to the function that is assigned.

Differences between the claims and the disclosure of Beach *et al.* (US 6,255,071)

Beach *et al.* discloses methods for identifying nucleic acid molecules that inhibit or influence a mammalian cellular function of interest. Beach *et al.* discloses vectors for screening test nucleic acids in methods for the identification and isolation of nucleic acid molecules based upon their ability to complement a mammalian cellular phenotype, antisense-based methods for the identification and isolation of nucleic acid sequences which inhibit the function of a mammalian gene, and gene trapping methods for the identification and isolation of mammalian genes that are modulated in response to specific stimuli. These methods either employ a single test nucleic acid sequence at a time (*see, e.g.*, col. 21, line 36 to col. 24, line 16) or libraries of nucleic acids (*see, e.g.*, col. 24, lines 38 to 51). The construction of the libraries used in the methods of Beach *et al.* involves cloning and amplification in bacteria, followed by purification prior to their introduction into host cells of interest (*see* Example 11, col. 39 to col. 42, line 5, in particular col. 39, lines 57-64). In one instance, Beach *et al.* discloses that the library may be amplified by PCR (*see* col. 41, lines 37-47) prior to its use in various methods. Beach *et al.* does not disclose directly amplifying and expressing an oligonucleotide family in the non-bacterial

host cell containing the target gene of interest. The cited passages of Beach *et al.* disclose that the libraries (oligonucleotide families) are constructed by (1) inserting the cDNA clones to be tested into an appropriate vector; **(2) transforming bacterial cells (*e.g., E. Coli*; *see* col. 40 line 5) to amplify the library or PCR amplification of the library (col. 41, lines 29-47); (3) purifying the amplified library;** and (4) packaging the library into expression vectors that transfect suitable target cells.

On the other hand, as discussed above, the library constructs that are elements of the instantly claimed methods are directly transfected into the target non-bacterial host cells that contain the gene to be analyzed. In fact, the absence of a bacterial cloning step or any prior amplification step is one of the advantages of the claimed methods of the instant application, providing savings in cost and time (*see, e.g.*, page 4, lines 27-29; page 13, lines 18-22). Unlike the methods disclosed in Beach *et al.*, in the instant methods, the family of nucleic acids used to identify gene function are ligated into a suitable vector, then immediately introduced into the target cell(s) that contain the gene(s) to be analyzed (*see, e.g.*, page 3, lines 10-22; page 4, lines 27-29; page 5, lines 21-27). Delivery, amplification and expression for genetic analysis are all carried out in a single system, avoiding prior bacterial (or other cellular) cloning steps and amplification steps.

Further, contrary to the Examiner's assertions, Beach *et al.* does not provide a method of assigning a function to a product encoded by a target nucleic acid by correlating a detectable phenotypic change with the function that is assigned. The first set of methods of Beach *et al.* cited by the Examiner describe identifying sequences that modulate genes whose associated phenotype is unknown (col. 22, lines 30-39; Example 15, col. 48). Therefore, unlike the instant methods, these methods of Beach *et al.* do not assign function

to a product encoded by a target nucleic acid by analyzing an associated phenotypic change, because the phenotype of the loss-of-function mutation within the gene is unknown. Thus, for example, in Example 15 (beginning at column 48, line 5), Beach *et al.* describes the preparation of a single gene antisense library of nucleic acid molecules that is screened for inhibition of expression of a target gene by monitoring the level of fluorescence of a reporter gene that has been fused to the target gene. Unlike the instant methods, no phenotypic change is analyzed for assignment of function.

Other methods cited by the Examiner are directed to newly identifying and isolating nucleic acid sequences that produce a cellular phenotype upon loss of function of an unknown gene (col. 24, lines 17-34) or that modulate a known phenotype such as cell survival (col. 27, lines 50-67) or a known gene such as telomerase (col. 48, line 54 to col. 49, line 20). These methods also do not assign a function to a product encoded by a nucleotide sequence of interest; rather, they are directed to newly identifying sequences that modulate a cellular effect of interest. Thus, for example, in Example 16 (beginning at column 48, line 53), Beach *et al.* discloses methods for the *in vitro* screening of a random cDNA library for nucleic acid molecules that induce a known phenotype, telomerase activity, in human mammary epithelial cells (HMECs). Here, pools of cDNAs (in the sense or antisense orientation) are introduced into HMEC cells and an individual clone that demonstrates an induction of telomerase activity is isolated (column 48, line 53, through column 49, line 20). The sequence of the isolated nucleic acid molecule represents a newly identified sequence from the cDNA library that induces a particular phenotype, namely, telomerase activity.

Thus, Beach *et al.* does not disclose every element of the claimed subject matter because Beach *et al.* does not provide a method of assigning a function to a product encoded by a target nucleotide sequence in which members of an

oligonucleotide family are directly introduced, amplified and expressed in a non-bacterial host cell containing the target sequence of interest, with no intervening bacterial cloning steps. Further, Beach *et al.* does not disclose a method of assigning a function to a product encoded by a sample nucleic acid sequence by analyzing a phenotypic change in the host cell containing a nucleic acid molecule containing the sample sequence and correlating the change with a corresponding function.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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